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Database:

US Patents Full-Text Database
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 JPO Abstracts Database
 EPO Abstracts Database
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 IBM Technical Disclosure Bulletins

Term:

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Display: Documents in Display Format: Starting with Number

Generate: Hit List Hit Count Side by Side Image

[Main Menu](#) | [Show S'Numbers](#) | [Edit S'Numbers](#) | [Preferences](#) | [Cases](#)

Search History

DATE: Wednesday, August 07, 2002 [Printable Copy](#) [Create Case](#)

<u>Set Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
		result set	
<i>DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ</i>			
<u>L6</u>	l2 and lipoprotein	56	<u>L6</u>
<u>L5</u>	l4 and (heart or coronary or cardiac)	18	<u>L5</u>
<u>L4</u>	methoxyflavone	65	<u>L4</u>
<i>DB=USPT; PLUR=YES; OP=ADJ</i>			
<u>L3</u>	l2 and flavanoid	18	<u>L3</u>
<u>L2</u>	L1 and (heart or cardiac)	168	<u>L2</u>
<u>L1</u>	flavone	801	<u>L1</u>

END OF SEARCH HISTORY

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L6: Entry 19 of 56

File: USPT

DOCUMENT-IDENTIFIER: US 6203818 B1

TITLE: Nutritional supplement for cardiovascular health

Abstract Text (1):

A nutritional supplement for improving cardiovascular health via aiding in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and coronary heart disease, the supplement comprising one or more flavonoids and folic acid or folate; and a method for aiding in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and coronary heart disease are described.

Brief Summary Text (2):

This invention relates to a nutritional supplement composition, more particularly, to a nutritional supplement composition that is intended to benefit cardiovascular health via aiding in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and coronary heart disease (CHD), and to a method for aiding in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and CHD by administration of the nutritional supplement composition to an individual.

Brief Summary Text (3):

According to the 1996 American Heart Association statistical summary, 42% of all deaths in America are from some form of cardiovascular disease. Since cardiovascular disease is the leading cause of death in the United States and many other developed countries, it is not surprising that heart specialists and physicians in general are frequently asked to provide advice concerning nutritional factors that may aid in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and CHD.

Brief Summary Text (4):

The use of vitamin and mineral supplements in one's diet is well established. Specifically, vitamin and mineral supplements heretofore devised and used for the purpose of providing daily nutrients are known to consist basically of familiar, predictable and obvious combinations. While many of the known supplements are adequate to fulfil their objectives, few have been specifically composed for improving cardiovascular health via aiding in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and coronary heart disease.

Brief Summary Text (5):

A number of synthetic drug formulations are available to maintain and benefit cardiovascular health or to treat or prevent atherosclerosis and coronary heart disease. Clofibrate, Gemfibrozil, Questran, Colestipol and HMG CoA reductase inhibitors are a few examples of synthetic drugs prescribed for decreasing cholesterol and triglyceride levels. All of the above-mentioned drugs have significant potential for side effects which include nausea, hepatic dysfunction, bone marrow suppression, gastrointestinal discomfort, heartburn, diarrhea, constipation, etc.

Brief Summary Text (7):

Given the above problems, there remains a need for a nutritional supplement that contains naturally occurring ingredients which can by design provide specific nutritional elements that available studies have shown provide potential benefit in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and coronary heart disease. The nutritional supplement of the invention is also expected to provide these benefits without anticipation of untoward side effects.

Brief Summary Text (10):

The present invention also provides a method for aiding in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and CHD which comprises the step of administering the nutritional supplement composition to an individual who is at risk or may be at risk of atherosclerosis and coronary heart disease.

Detailed Description Text (2):

The present invention provides a composition which is useful as a nutritional supplement to aid in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and coronary heart disease. The composition of the present invention is a combination of one or more flavonoids and folic acid or folate. The combined use of these two supplements is believed to respond to some, if not most, of the common conditions implicated in cardiovascular disease such as platelet aggregation, oxidation of blood lipids in arterial walls, and elevated homocysteine levels. These agents may be combined in an oral dosage with other well known nutritional supplements and/or non-flavonoid antioxidants, e.g., selenium, vitamin E (tocopherol, particularly *alpha*-tocopherol, etc.), vitamin C (ascorbic acid) and coenzyme Q10. Dietary fiber supplements may also be used in the composition.

Detailed Description Text (3):

Flavonoids, also known as "phenylchromones," are naturally occurring, water-soluble compounds which have antioxidant characteristics. Flavonoids are widely distributed in vascular plants and are found in numerous vegetables, fruits and beverages such as tea and wine (particularly red wine) and, therefore, are a common component of the human diet. The animal kingdom is unable to synthesize the flavone nucleus; flavonoids are therefore strictly exogenous food components of plant origin.

Detailed Description Text (5):

where R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7 and R.sup.8 are independently selected from H and OR' where R' is H or an alkyl group having about 1 to 10 carbon atoms. As of the mid 1980's more than 4000 chemically unique flavonoids have been identified and this is only a fraction of the total number likely to be present in nature. The most widely occurring flavonoids are flavones and flavonols. While the present invention is open to the use of all flavonoids, flavonols and more particularly, myricetin, (3,5,7,3',4',5',-hexahydroxyflavone), quercetin (3,5,7,3',4'-pentahydroxyflavone), kaempferol (3,5,7,4'-tetrahydroxyflavone), and flavones apigenin (5,7,4'-trihydroxyflavone) and luteolin (5,7,3',4'-tetrahydroxyflavone) and glycosides thereof are preferred. The most preferred flavonoid for use in the invention is quercetin.

Detailed Description Text (6):

It is believed that quercetin, which exhibits some of the strongest antioxidant effects of the flavonoids and which has been reported to inhibit oxidation and cytotoxicity of low density lipoproteins (LDL), may have beneficial health consequences since oxidized low density lipoproteins are reported to be atherogenic, i.e., they contribute to the buildup of fatty substances in the arterial wall. Lipid peroxidation is caused by free radicals. Free radicals are molecules with at least one unpaired electron, which makes them highly reactive. Free radicals are continually formed in the metabolic processes of the human body but are tightly regulated. Human plasma contains various antioxidants which makes it difficult for such reactions to occur within the plasma. When LDL is within the arterial wall, the situation is different and the plasma antioxidant protection is not available. The reaction that can result in buildup of oxidized lipids in the arterial wall can be stopped or decreased by the presence of an antioxidant such as a flavonoid. Flavonoids appear to act by protecting LDL against oxidation, as they inhibit the generation of lipid peroxides and also may help protect *alpha*-tocopherol (vitamin E), a major lipophilic antioxidant carried in lipoproteins, from being consumed by oxidation in LDL.

Detailed Description Text (9):

Folic acid is a B complex vitamin. It is water-soluble and occurs naturally in green plants, fresh fruit, and yeast. Folic acid along with vitamins B.sub.12 (cyanocobalamin) and B.sub.6, plays a key part in homocysteine metabolism. Medical studies have demonstrated that there is a statistically significant positive correlation between total plasma homocysteine levels and the incidence of atherosclerosis and coronary heart disease. Men whose homocysteine levels are known to

be significantly elevated are more likely to suffer myocardial infarction. Also, it has been demonstrated that inadequate folic acid or folate intake is the main determinate of the homocysteine-related increase in carotid artery thickening, another significant manifestation of atherosclerotic disease. The mechanism by which elevated blood homocysteine causes accelerated atherosclerosis has not been clearly established. U.S. population dietary surveys have demonstrated that up to 40 percent of the population may not consume enough folic acid to prevent elevated blood homocysteine levels. Folic acid or folate supplements in the range of 0.4 to 2 mg. per day are usually sufficient to reduce or normalize high homocysteine levels. The folic acid or folate of the nutritional supplement may be administered in a daily dose of about 0.1 to 10 mg. and, more typically, about 0.4 to 1 mg.

Detailed Description Text (14):

In addition to providing the aforementioned compositions, the invention also includes a method for orally administering the composition in dosages effective to aid in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and coronary heart disease and, more particularly, to a method for orally administering the aforesaid composition to an individual who is at risk of or may be at risk of atherosclerosis and coronary heart disease. The supplement is preferably administered orally but may be administered parenterally. Suitable forms for the nutritional supplement composition for oral or parenteral administration include tablets, capsules, lozenges, syrups, granules, solutions and suspensions which contain unit doses of the supplement for administration once or several times a day. The nutritional supplement composition of the invention will typically be administered orally as a tablet or a capsule. Tablets, gel tabs, capsules, liquid and sustained release formulations can be formulated and prepared according to manufacturing techniques well known in the pharmaceutical industry and in a variety of dosage forms.

Other Reference Publication (13):

Catherine V. deWhalley et al., Flavonoids Inhibit the Oxidative Modification of Low Density Lipoproteins by Macrophages, Biochemical Pharmacology, vol. 39, No. 11, pp. 1743-1750, 1990.

Other Reference Publication (17):

E.N. Frankel, Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine, The Lancet, vol. 341: Feb. 20, 1993, pp. 454-457.

Other Reference Publication (18):

Michael G.L. Hertog et al., Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study, The Lancet, vol. 342, Oct. 23, 1993, pp. 1007-1011.

Other Reference Publication (21):

L. Daly et al., Hyperhomocysteinaemia: a metabolic risk factor for coronary heart disease determined by both genetic and environmental influences?, Quarterly Journal of Medicine, 1993; 86:685-689.

Other Reference Publication (22):

Brief Critical Reviews, Dietary Flavonoids and Risk of Coronary Heart Disease, Nutrition Reviews, vol. 52, No. 2, Feb. 1994: 59-68.

Other Reference Publication (28):

Andrew G. Bostom et al., High dose ascorbate supplementation fails to affect plasma homocyst(e)ine levels in patients with coronary heart disease, Atherosclerosis 111 (1994) 267-270.

Other Reference Publication (32):

Michael G.L. Hertog et al., Flavonoid Intake and Long-term Risk of Coronary Heart Disease and Cancer in the Seven Countries Study, Arch Intern Med, vol. 155, pp. 381-386, Feb. 27, 1995.

Other Reference Publication (33):

Jiri J. Frohlich, Lipoproteins and homocyst(e)ine as risk factors for atherosclerosis: Assessment and treatment, Can J Cardiol, vol. II, Suppl C, May 1995, pp. 18C-23C.

Other Reference Publication (43):

Cecil R. Pace-Asciak et al., The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: Implications for protection against coronary heart disease, Clinica Chimica Acta 235 (1995) 207-219.

Other Reference Publication (46):

Johan B. Ubbink et al., Effective homocysteine metabolism may protect South African blacks against coronary heart disease, Am J Clin Nutr, 1995 62:802-8.

Other Reference Publication (49):

Egil Arnesen et al., Serum Total Homocysteine and Coronary Heart Disease, International Journal of Epidemiology, vol. 24, No. 4, 1995, pp. 704-709.

Other Reference Publication (50):

A.F.E. Rump et al., Effects of Different Inotropes with Antioxidant Properties on Acute Regional Myocardial Ischemia in Isolated Rabbit Hearts, Gen. Pharmac., vol. 26, No. 3, pp. 603-611, 1995.

Other Reference Publication (55):

Howard I. Morrison et al., Serum Folate and Risk of Fatal Coronary Heart Disease, JAMA, Jun. 26, 1996, vol. 275, No. 24, pp. 1893-1896.

Other Reference Publication (57):

Paula M. Gallagher et al., Homocysteine and Risk of Premature Coronary Heart Disease (Evidence for a Common Gene Mutation), Circulation, vol. 94, No. 9, Nov. 1, 1996, pp. 2154-2158.

Other Reference Publication (58):

Barry C. Herzlich et al., Relationship among Homocyst(e)ine, Vitamin B-12 and Cardiac Disease in the Elderly: Association between Vitamin B-12 Deficiency and Decreased Left Ventricular Ejection Fraction, American Institute of Nutrition, 1996, pp. 1249S-1253S.

Other Reference Publication (59):

Johan B. Ubbink et al., Plasma Homocysteine Concentrations in a Population with a Low Coronary Heart Disease Prevalence, American Institute of Nutrition, 1996, pp. 1254S-1257S.

CLAIMS:

8. A method for aiding in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and coronary heart disease in a person comprising the step of administering to said person a nutritional supplement including quercetin and folic acid or folate wherein said supplement is administered in an amount which provides a daily dosage of quercetin of about 0.1 to 500 mg and a daily dosage of folic acid or folate of about 0.1 to 10 mg.

16. A method for aiding in preventing, delaying the onset of and/or slowing the progression of atherosclerosis and coronary heart disease in a person comprising the step of administering to said person a nutritional supplement including quercetin, folic acid or folate, and a dietary fiber supplement wherein said quercetin is present in an amount which provides a daily dosage of about 0.1 to 500 mg and said folic acid or folate is present in an amount which provides a daily dosage of about 0.1 to 10 mg.